Monotherapy of topical tacrolimus 0.03% in the treatment of vernal keratoconjunctivitis in the pediatric population

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PURPOSE To report the results of treating children with vernal keratoconjunctivitis (VKC) using a monotherapy of topical tacrolimus 0.03%.

METHODS This was a prospective, nonrandomized observational study of children newly diagnosed with VKC. The severity of the disease was graded on a 4-point scale of symptoms and signs. Patients were treated with tacrolimus 0.03% ointment and were followed for 8 months according to a schedule based on the severity of the disease. The primary measure of treatment efficacy was the change in the score of objective signs. The incidence and severity of adverse events, if any, were recorded.

RESULTS A total of 45 children aged 5-15 years were enrolled. The mean composite symptom score was 6.84 ± 2.26 at baseline and 0.71 ± 1.62 at 8 months, a statistically significant reduction ($P < 0.001$). The mean composite sign score was 9.6 ± 3.14 at baseline and 1.16 ± 1.28 at 8 months, also a statistically significant reduction ($P < 0.001$). Four patients had to be started on steroids within the first month of treatment and were considered treatment failures. Thus, 89% of patients showed significant improvement. No participant experienced adverse effects, although some reported a transient stinging sensation.

CONCLUSIONS In our study cohort topical tacrolimus ointment 0.03% as a monotherapy for VKC was successful in the majority of subjects, and there was no adverse effect. (J AAPOS 2019;23: 36.e1-5)

Vernal keratoconjunctivitis (VKC) is a severe form of chronic, bilateral, allergic conjunctivitis that affects the ocular surface. It is seen commonly in children and adolescents who are predisposed by their atopic background. Disease onset usually occurs before 10 years of age and predominantly affects males. VKC usually worsens seasonally. An inflammatory process mediated by the CD4+T helper cell 2 (Th-2) has been implicated in the pathogenesis. The disease manifests in three forms: tarsal, limbal, and mixed. Symptoms include burning sensation, itching, perceived redness, watering, and photophobia, with associated lid swelling. Signs include tarsal papillae, Horner-Trantas dots, punctate epithelial keratitis and epithelial defects, shield ulcers, and pseudogerontoxon. Active shield ulcers, severe annular limbal inflammation, limbal stem cell deficiency manifesting as extensive conjunctivalization, limbal scarring, and extensive corneal scarring are blinding complications. Sequelae include tarsal scarring, dry eyes, and eyelid malpositions.

Avoidance of allergen, mast-cell targeted therapy and antihistamines are, however, effective in the early pathogenetic phases, but once T-cell mediated reactions set in, these may no longer suffice, and a vicious cycle follows. Topical steroids are indicated for severe exacerbations, but its long-term use is associated with complications such as cataracts and glaucoma. VKC in the warm temperatures zones are associated with a chronic course that warrants a longer duration of therapy.[1] Topical cyclosporine has been used in different concentrations with varying results. The side effects noted were a bothersome burning sensation and ocular pain upon application. Tacrolimus is a macrolide antibiotic immunomodulator isolated from *Streptomyces tsukubaensis*[2] used in the treatment of VKC. It binds to FK-506 binding proteins in the T-lymphocytes and inhibits calcineurin activity. This suppresses dephosphorylation of the nuclear factor of the activated T cells and its transfer into the nucleus, which suppresses the formation of Th1 and Th2 cytokines. It inhibits the release of histamine from the mast cells[3] as well. Tacrolimus is nearly 100 times more potent[4] than cyclosporine, with only a transient burning sensation. The successful off-label use of tacrolimus to treat a range of ophthalmic conditions has been reported.[5,6] Although small studies have

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Submitted March 14, 2018.
Revision accepted September 28, 2018.
Published online January 19, 2019.
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1091-8531/$36.00
https://doi.org/10.1016/j.jaapos.2018.09.010

demonstrated the efficacy of tacrolimus in VKC,[6,7] significant failure has also been reported.[8] In the current study, the outcome of monotherapy with tacrolimus ointment 0.03% in cases of VKC in the pediatric age group was studied. The purpose of the current study was to investigate a monotherapy of topical tacrolimus 0.03% ointment in the treatment of VKC in pediatric population in a tertiary eye care center in South India.

Subjects and Methods

This was a prospective, nonrandomized observational study of consecutive pediatric patients attending the pediatric clinic at Aravind Eye Hospital, Tirunelveli, Tamil Nadu, over a period of 8 months, from December 2016 to August 2017. This study was approved by the Aravind Eye Care System Institutional Research Board, Madurai, and adhered to the recommendations of the Declaration of Helsinki. Informed consent was obtained from the parents of the study participants. Inclusion criteria were all new and previously untreated cases diagnosed as VKC of varying severity, cases of VKC refractory to conventional antiallergic therapy (antihistamines, mast cell stabilizers, steroids), cases in which there was a relapse after withdrawal of steroids, and cases in which steroid-related complications developed. Exclusion criteria were history of contact lens usage, coexisting ocular infections, past history of ocular surgery, history of herpetic eye disease, and known hypersensitivity to tacrolimus.

All the subjects diagnosed with VKC received comprehensive ophthalmic examinations at each visit, including slit-lamp examination, estimation of best-corrected visual acuity, and measurement of intraocular pressure by noncontact tonometry. All participants were started on 0.03% tacrolimus ointment (Tacliment 0.03%; Aurolab, Madurai, India).

Disease severity was graded as mild, moderate, or severe based on a four-point scale of symptoms and signs (Table 1, modified from previously published studies).[7] The patients were instructed to instill an amount about the size of a rice grain in the conjunctival cul-de-sac according to a schedule based on the severity of the disease (Table 2). The composite score of symptoms and signs was made at the time of enrollment and subsequent follow-up visits at 2 weeks, 1 month, 3 months, and 8 months. In the case of bilateral disease, the eye with a higher sign score at initial presentation was taken for grading of the disease and for statistical analysis, even though the treatment protocol was the same for both the eyes. The primary measure of treatment efficacy was a lower final score of objective signs. Symptom scoring helped to assess subjective improvement over the course of follow-up. Failure of treatment was defined as additional requirement of topical steroids to control the inflammation even after 1 month of starting treatment with tacrolimus 0.03%.

Patients and parents were instructed to report the ability to tolerate the medication and to report any adverse effects. The changes in clinical score from the baseline visit to the visit at 2 weeks, 1 month, 3 months, and 8 months were compared by paired *t* test and Wilcoxon signed-rank test. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA 11.1 (Statacorp, College Station, TX).

Table 1. Scores for clinical symptoms and signs

Symptoms and severity	Score
Burning	
Absent	0
Mild	1+
Moderate	2+
Severe	3+
Discharge	
Absent	0
Mucoid discharge in the lower cul-de-sac	1+
Moderate	2+
Matted lids requiring frequent cleaning	3+
Itching	
No need to itch	0
Occasional itching	1+
Frequent itching	2+
Constant itching	3+
Photophobia	
Absent	0
Sensitivity to sunlight but can open eyes	1+
Sensitivity/intolerance to sunlight: eyes cannot be kept open for long	2+
Intolerance to sunlight: avoidance and inability to open eyes	3+
Perceived redness	
Absent	0
Detected only on close observation	1+
Detectable at near	2+
Detectable at distance	3+
Watering	
Normal tear production	0
Waterlogged feeling	1+
Infrequent spilling of tears	2+
Constant spilling of tears	3+
Clinical signs/severity	**Score**
Conjunctival fibrosis	
No scar	0
Subepithelial fibrosis	1+
Fornix shortening	2+
Symblepharon	3+
Conjunctival hyperemia	
Absent	0
Dilation of some blood vessels (1 quadrant)	1+
Dilation of several blood vessels (<1 quadrant)	2+
Generalized dilation of blood vessels	3+
Horner-Trantas dots	
None	0
1-3	1+
4-6	2+
6	3+
Limbal inflammation	
None	0
1 quadrant	1+
2 quadrants	2+
3-4 quadrants	3+
Punctate keratopathy	
Intact epithelium	0
Punctate in 1/3 of cornea	1+
Punctate in 2/3 of cornea	2+
Diffuse punctate	3+
Tarsal papillary reaction	0
No papillae	1+
Papillary reaction without giant papillae	2+
Some giant papillae	3+
Giant papillae all over the tarsal conjunctiva	

Table 2. Disease severity and dosage schedule

Sign score	Disease severity	Dosage schedule
1-6	Mild	Once daily 2 mos
7-12	Moderate	Twice daily for 1 mo, then once daily for 2 mos
>12	Severe	Twice daily for 2 mos, then once daily for 2 mos, then once every other day for 1 mo

Results

Of the 60 patients enrolled in the study, only 45 (37 males [82%]) were available for analysis; 11 patients were lost to follow-up, and 4 patients were excluded due to poor treatment compliance. The mean age at treatment was 8.23 ± 2.7 years (standard deviation); the age range was 5-14 years.

Two patients had a pure palpebral type of VKC, whereas 43 had a mixed type of VKC. According to the baseline composite sign score, 6 patients had mild VKC; 25, moderate; and 14, had severe.

The mean scores for the symptoms and signs at initial visit and subsequent follow-up visits are shown in Figures 1 and 2. The mean composite symptom score at baseline was 6.84 ± 2.26 and fell to 0.71 ± 1.62 at 8 months ($P < 0.001$). The mean composite sign score at baseline of 9.6 ± 3.14 fell to at 8 months to 1.16 ± 1.28 ($P < 0.001$).

Table 3 and Figure 3 show the response shown by previously untreated and refractory cases to the monotherapy. Both previously untreated and refractory cases responded equally to tacrolimus 0.03% monotherapy, with scores being clinically and statistically significant.

Itching was the first symptom to resolve in the first follow-up visit at 2 weeks in the majority of the patients (67%). The next to resolve was redness (24.4%).

There was no significant change in the mean intraocular pressure from baseline 14.23 ± 2.8 to 13.22 ± 1.9 at month 8.

The mean logMAR best-corrected visual acuity improved from a baseline value of 0.03 ± 0.07 to 0.01 ± 0.04 at month 8 ($P = 0.046$).

Three patients developed recurrence of symptoms about 2 weeks after completing the course of treatment.

Four patients, 2 with severe VKC and 2 with moderate VKC, had to be started on steroids within 4 weeks of starting treatment; these cases were considered treatment failures. One patient who failed to respond developed subepithelial keratitis. There was no adverse effect other than a transient stinging sensation reported by the participants.

Discussion

In severe ocular allergy like VKC that require long-term therapy, antiallergic drugs are often insufficient, and concomitant use of steroids is associated with the risk of iatrogenic cataract and glaucoma.[8] Cyclosporine has been a useful alternative treatment, but results have been inconsistent, and patients experience a burning sensation. The immunomodulatory functions of tacrolimus, mainly the prevention of formation of cytokines[9] and the inhibition of release of histamines,[3] have been exploited in the

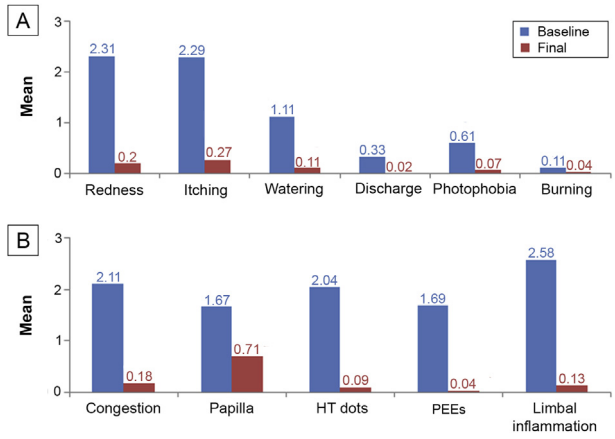

FIG 1. A, Mean symptom score at presentation through all follow-up visits. B, Mean sign score at presentation through all follow-up visits. *HT dots*, Horner-Trantas dots; *PEE*, punctate epitheial erosions.

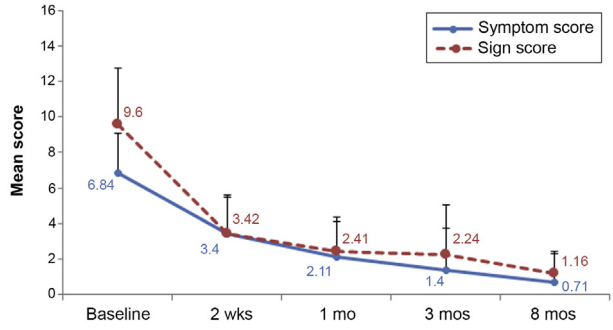

FIG 2. Comparison of composite symptom score and sign score over the entire period of follow-up.

Table 3. Before and after-treatment comparisons between the baseline and final visits in previously untreated patients and those refractory to other treatment modalities

	Untreated, mean ± SD	Refractory, mean ± SD	Overall, mean ± SD	*P* value[a]
Symptom score				
Baseline	6.45 ± 1.99	7.22 ± 2.47	6.84 ± 2.26	0.333
2 weeks	3.23 ± 2.16	3.57 ± 2.02	3.40 ± 2.07	0.636
1 months	2.00 ± 1.98	2.22 ± 2.09	2.11 ± 2.01	0.702
3 months	1.00 ± 1.02	1.78 ± 3.07	1.40 ± 2.32	0.743
8 months	0.95 ± 2.17	0.48 ± 0.79	0.71 ± 1.62	0.857
P value[d]	0.0001	<0.001	<0.001	—
Sign score				
Baseline	9.50 ± 3.25	9.70 ± 3.10	9.60 ± 3.14	0.899
2 weeks	3.68 ± 2.30	3.17 ± 2.04	3.42 ± 2.16	0.389
1 months	2.82 ± 2.30	2.00 ± 1.41	2.41 ± 1.93	0.270
3 months	1.86 ± 1.75	2.61 ± 3.51	2.24 ± 2.79	0.972
8 months	0.95 ± 1.36	1.35 ± 1.19	1.16 ± 1.28	0.086
P value[b]	<0.001	<0.001	<0.001	—

[a]Mann-Whitney U test.
[b]Wilcoxon sign rank test.

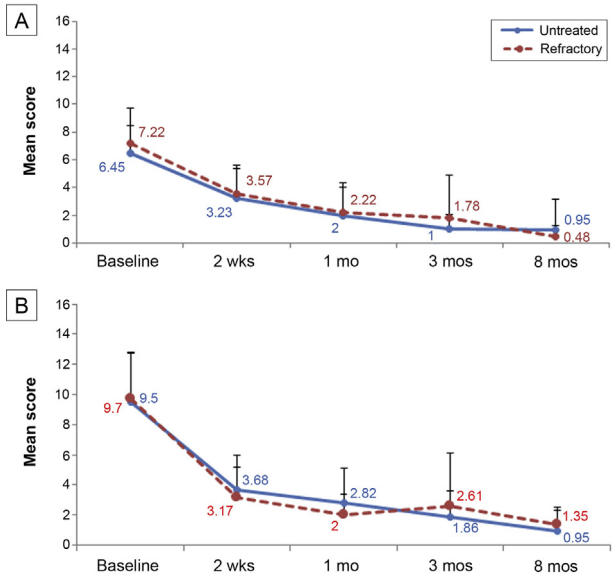

FIG 3. A, Composite symptom scores of the previously untreated and the refractory groups. B, Composite sign scores of the previously untreated and the refractory groups.

management of ocular allergy and have been extensively investigated.

In the current study, monotherapy with tacrolimus 0.03% successfully managed VKC in 89% of patients, who showed significant improvement in symptoms and signs. The composite sign score significantly reduced from baseline values, and patients reported relief from itching in as early as 2 weeks, with associated improvement in visual acuity, most likely due to resolution of corneal erosions from constant itching and subsidence of excessive lacrimation. Kheirkah and colleagues[10] reported that itching was also the first symptom to resolve in their study, and that bulbar congestion was the first sign to resolve. Early relief of itching in VKC with timely treatment is associated with the long-term benefit of lower risk of developing myopic astigmatism and keratoconus. In our study, the resolution of tarsal papillae and cobblestone papillae were delayed compared to symptomatic improvement in itching. Kymnios and colleagues[5] found that tacrolimus 0.03% monotherapy reduced giant papillae in as early as 2 weeks in giant papillary conjunctivitis.

Chatterjee and colleagues[7] demonstrated a successful outcome with topical tacrolimus 0.03% ointment in addition to topical ketotifen 0.05% eye drops and 0.05% carboxy methyl cellulose eye drops on 30 patients with corticosteroid refractory VKC in patients with a mean age of 14 ± 6.4. The composite scores for symptoms and signs in their study[7] showed a statistically significant improvement from baseline to the final follow-up at 3 months ($P < 0.05$), and the treatment was successful in >80% of patients. The only adverse effect reported was a stinging sensation on application, which was reported by our patients as well. However, our study was restricted to the pediatric patients, was a monotherapy, and had a relatively longer follow-up period.

Favorable outcomes have also been recorded with tacrolimus 0.1%. In the multicenter, randomized clinical trial by Ohashi and colleagues,[11] tacrolimus 0.1% ophthalmic suspension was administered twice daily for 4 weeks in 21 patients with AKC and 7 patients with VKC. Treated eyes (compared to untreated controls) showed marked clinical improvement after 4 weeks. Concomitant use of topical or systemic antiallergic agents was allowed in this study. The incidence of treatment-related adverse events, including ocular irritation, was significantly higher ($P = 0.044$) in the tacrolimus group (46.4% [13/28]) than in the placebo group (17.9% [5/28]). In this study, there was 1 case of suspected herpetic keratitis in the tacrolimus group and another case of hordeolum in the placebo group.

In the prospective, nonrandomized study by Al-Amri and colleagues[12] to evaluate the use of tacrolimus 0.1% ointment for the treatment of VKC, 20 patients 9-21 years were studied over 2 years. Significant improvement in clinical signs and symptoms were achieved in all patients 6 weeks after starting treatment. Long-term use of tacrolimus was needed to control recurrence of the disease, because discontinuation of therapy was found to be associated with the recurrence of symptoms. Longer follow-up data were reported by Pacharn and colleagues,[13] where tacrolimus 0.1% was successfully used for 3 years in patients with VKC.

Four patients had treatment failure as defined in our study, in whom topical steroids had to be added within 1 month of starting Tacrolimus 0.03% monotherapy. Tam and colleagues,[6] in their case series, reported the use of additional therapy with mast-cell stabilizers and steroids in VKC. Fukushima and colleagues,[8] in their study, showed that 53.4% of patients with refractory allergic ocular diseases with proliferative lesion or corneal involvement using steroids were successfully weaned from topical steroid therapy with 0.1% Tacrolimus eye drops.

A newly identified cytokine, thymic stromal lymphopoietin (TSLP), has been reported to activate dendritic cells, which in turn primes naive T cells to produce proallergenic cytokines in a TH2 response in atopic dermatitis[14] and chronic allergic conjunctivitis.[15] Cyclosporine and tacrolimus have been found to be less effective[16,17] in suppressing the release of this cytokine in experimental models, whereas dexamethasone was observed to completely suppress its release.[16] This could explain the reason why some patients fail to respond to immunomodulators and require steroids.

The only adverse effect in our study cohort was a transient stinging sensation with the drug, which was otherwise well-tolerated by most participants. The stinging sensation has been documented with use of tacrolimus in previously published studies with higher concentrations (0.01%)[8,11] and not with 0.005%,[10] suggesting that this reaction could depend on the concentration of the drug. In our study,

there was no significant adverse effect during the course of treatment that mandated discontinuation of therapy.

Fukushima and colleagues[8] reported bacterial keratitis, corneal ulcer, and herpetic keratitis as adverse events with tacrolimus therapy in refractory allergic ocular diseases, thus emphasizing the importance of close monitoring of patients on tacrolimus. T-cell lymphoma has been reported,[18] with insufficient epidemiological evidence however, with the use of topical tacrolimus 0.1% in higher cumulative doses (75 g) in atopic dermatitis and eczema, where there is significant percutaneous absorption of the drug, over a follow-up period of 2.4 years. However, it was concluded that the theoretical cancer risk from exposure is low because no evidence of systemic accumulation was observed after repeated application of the drugs. Renal failure is a systemic side effect of tacrolimus. No systemic side effect were noted in our study. The percentage of tacrolimus reaching the bloodstream with twice-daily topical dosage of tacrolimus has been shown to be very low.[19,20] Tacrolimus is not recommended in patients younger than 2 years; the US Food and Drug Administration has warned that use of tacrolimus and pimecrolimus ointment in the treatment of atopic dermatitis may cause cancer.[21] In view of this, our study was carried out in 5- to 15-year-age-olds.

The optimum dose and duration of treatment must be further consolidated by randomized studies over a longer period of time, because recurrence of symptoms was noted in 3 subjects in our study after 8 months. The long-term side effects must be investigated too; most of the previously published studies have not reported treatment or follow-up beyond 6 months.[10,22] Hence, the smaller sample size and shorter duration of treatment are the limitations of our study. Nevertheless, our results indicate that early inclusion of low-strength tacrolimus (0.03%) in the management protocol of pediatric patients with VKC can prevent the development of blinding sequelae of the disease and holds promise as a long-term therapy.

Acknowledgments

The authors thank Ramalakshmi Raman, and Mohammed Sithiq Uduman Sheik Meeran for their assistance.

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